Claims

1. A process for the preparation of crystalline (6RS)-N(5)-formyl-5,6,7,8-tetrahydrofolic acid or of amorphous (6S)-N(5)-formyl-5,6,7,8-tetrahydrofolic acid,

characterized in that there is added to stirred water having a temperature from 2°C to 12°C simultaneously

- an aqueous solution having a temperature from 40°C to 50°C of (6RS)- or of (6S)-calcium-folinate, and

- an aqueous solution of hydrochloric acid or of acetic acid

in such a way that in the obtained mixture during the addition of both of said solutions on one hand the temperature is kept at a value from 2°C to 12°C and on the other hand the pH value is kept at a value from 2.5 to 3.5,

the formed solid is isolated by means of filtration or centrifugation,

this solid is washed first with cold water and then with an aqueous organic solvent, and

the washed solid, that is crystalline (6RS)-N(5)-formyl-5,6,7,8-tetrahydrofolic acid or amorphous (6S)-N(5)-formyl-5,6,7,8-tetrahydrofolic acid, is dried under reduced pressure and is obtained.

2. The process according to claim 1, characterized in that the stirred water, to which said two solutions are added simultaneously, has a temperature from 6°C to 10°C.

3. The process according to one of claims 1 to 2, characterized in that the aqueous solution of (6RS)-calcium-folinate has a concentration from 7.5 % by weight to 8.5 % by weight.

4. The process according to one of claims 1 to 2, characterized in that the aqueous solution of (6S)-calcium-folinate has a concentration from 3.0 % by weight to 3.7 % by weight, preferably 3.5 % by weight.

5. The process according to one of claims 1 to 4, characterized in that the aqueous solution of (6RS)- or of (6S)-calcium-folinate has a temperature of 46°C.

6. The process according to one of claims 1 to 5, characterized in that the aqueous solution of hydrochloric acid has room temperature and has a concentration from 10 % by weight to 20 % by weight, preferably 18 % by weight.

7. The process according to one of claims 1 to 6, characterized in that in the obtained mixture during the simultaneous addition of both of said solutions the temperature is kept at a value from 6°C to 10°C.

8. The process according to one of claims 1 to 7, characterized in that in the obtained mixture during the simultaneous addition of both of said solutions the pH value is kept at a value from 2.8 to 3.2.

9. The process according to one of claims 1 to 8, characterized in that after the realized simultaneous addition of both of said solutions the obtained mixture is stirred for 1 additional hour at a temperature from 6°C to 10°C.

10. The process according to one of claims 1 to 9, characterized in that

- in the case of the use of (6RS)-calcium-folinate as starting material the formed crystalline solid is washed after the washing with cold water with a 9:1 mixture (v/v) of acetone and water, and that

- in the case of the use of (6S)-calcium-folinate as starting material the formed amorphous solid is washed after the washing with cold water with a 94:6 mixture (v/v) of ethanol and water.

11. Crystalline (6RS)-N(5)-formyl-5,6,7,8-tetrahydrofolic acid and amorphous (6S)-N(5)-formyl-5,6,7,8-tetrahydrofolic acid.

12. Crystalline (6RS)-N(5)-formyl-5,6,7,8-tetrahydrofolic acid and amorphous (6S)-N(5)-formyl-5,6,7,8-tetrahydrofolic acid according to claim 11, characterized in that these two compounds have been prepared according to the process according to one of claims 1 to 10.

13. Use of crystalline (6RS)-N(5)-formyl-5,6,7,8-tetrahydrofolic acid or of amorphous (6S)-N(5)-formyl-5,6,7,8-tetrahydrofolic acid for the preparation of an aqueous solution of the sodium or potassium salt of (6RS)- or (6S)-folinic acid.

14. A process for the preparation of a concentrated, stable solution, especially of an injection solution or of an infusion solution, of the sodium or potassium salt of (6RS)- or (6S)-folinic acid,

characterized in that crystalline (6RS)-folinic acid or amorphous (6S)-folinic acid is suspended in water, that is degassed and that is acceptable for the preparation of injection solutions or of infusion solutions, at room temperature under an inert gas atmosphere, then

an aqueous solution of sodium or potassium hydroxide, -hydrogencarbonate or -carbonate is added in portions during such a long time until a clear solution is formed having the respective desired pH value,

the obtained solution is subjected to a sterile filtration, and

the obtained sterile solution is filled into vials or into ampoules under an inert gas atmosphere.

15. The process according to claim 14, characterized in that the crystalline (6RS)-folinic acid or the amorphous (6S)- folinic acid is prepared according to the process according to one of claims 1 to 10.

16. The process according to one of claims 14 to 15, characterized in that said clear solution contains from 2 % by weight to 15 % by weight, especially from 2 % by weight to 6 % by weight, preferably 5 % by weight, of (6RS)- or (6S)-sodium-folinate or of (6RS)- or (6S)-potassium-folinate.

17. The process according to one of claims 14 to 16, characterized in that said clear solution has a pH value in the range from 7.5 to 8.5, especially from 7.9 to 8.1, preferably 8.0.

18. Concentrated, stable solution, especially an injection solution or an infusion solution, characterized in that it contains beside water either (6S)-sodium-folinate or (6S)-potassium-folinate.

19. Solution according to claim 18, characterized in that it is prepared according to the process according to one of claims 14 to 17.

20. Solution according to one of claims 18 to 19, characterized in that it contains from 2 % by weight to 15 % by weight, especially from 2 % by weight to 6 % by weight, preferably 5 % by weight, of (6S)-sodium-folinate or (6S)-potassium-folinate.

21. Solution according to one of claims 18 to 20, characterized in that it has a pH value in the range from 7.5 to 8.5, especially 7.9 to 8.1, preferably 8.0.

22. Solution according to one of claims 18 to 21, characterized in that it contains neither a stabilizer nor a complexing agent.

23. Solution according to one of claims 18 to 22, characterized in that it is filled into vials or into ampoules having in their interior an inert gas atmosphere, especially a nitrogen atmosphere.

24. Vials or ampoules, characterized in that there is filled into them a concentrated, stable solution according to one of claims 18 to 23.

25. Use of the solution according to one of claims 18 to 23 for the preparation of a medicament for rescues - rescue agent - after the treatment with high doses of methotrexate.

26. Use of the solution according to one of claims 18 to 23 for the preparation of a medicament which is combined with 5-fluorouracil.

27. Use of the solution according to one of claims 18 to 23 for the preparation of a medicament for the treatment of megaloblastic anemia and dihydropteridin reductase deficiency.